Patent
Attorney Docket No: AM-00102.P.1-US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	
Efimov et al.	Examiner: To be determined
	Group Art Unit: To be determined
Application Number: To be determined	
Filed: Herewith	
For: OLIGONUCLEOTIDE ANALOGUES, METHODS OF SYNTHESIS AND METHODS OF USE	

Assistant Commissioner for Patents
Washington D.C., 20231

Sir,

PRELIMINARY AMENDMENT NO. 1

Prior to examination, please amend the application as provided below:

IN THE CLAIMS

Please cancel all of the claims, claims 1 through 96.
Please add the following claims, claims 97 through 129.
Thus, claims 97 through 129 are pending upon entry of this amendment.

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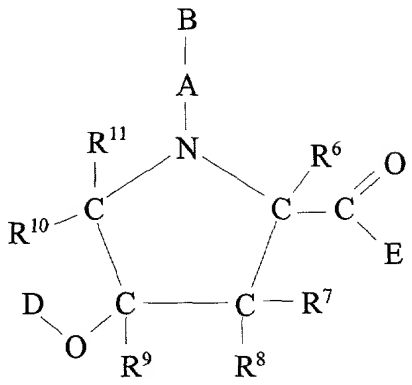
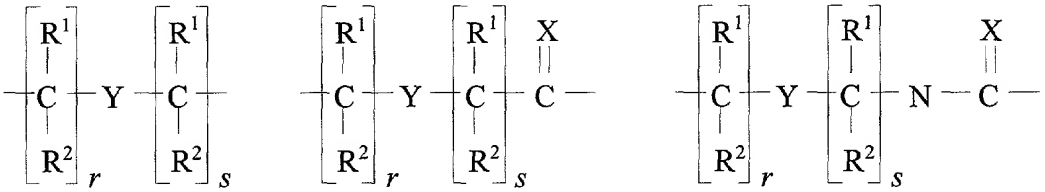
97. A compound comprising the structure:



wherein B is H, a naturally occurring nucleobase, a non-naturally occurring nucleobase, an aromatic moiety, a DNA intercalator, a nucleobase-binding group, a heterocyclic moiety, or a reporter group, wherein amino groups are, optionally, protected by amino protecting groups;

wherein A is a group of formula (Ia), (Ib), or (Ic);



I(a) I(b) I(c)

wherein *r* and *s* are, for I(a) and I(b), independently of one another, values from 0 to 5 and are, for I(c), independently of one another, values from 1 to 5;

wherein each R^1 and each R^2 is, independently, hydrogen, (C_1 –C_6)alkyl, hydroxy-, alkoxy-, amino-, or alkythio-substituted (C_1 –C_6)alkyl, hydroxy, alkoxy, alkylthio, amino, or halogen;

wherein each of R^3, R^4, and R^5, is, independently, hydrogen, (C_1 –C_6)alkyl, hydroxy-, alkoxy-, amino-, or alkythio-substituted (C_1 –C_6)alkyl, hydroxy, alkoxy, amino, aryl, aralkyl, heteroaryl, or an amino acid side chain;

Y is a single bond, O, S, or NR^4; and

X is O, S, Se, NR^5, CH_2, or $C(CH_3)_2$;

wherein R^6 is hydrogen, (C_1 –C_6)alkyl, hydroxy-, alkoxy-, amino-, or alkythio-substituted (C_1 –C_6)alkyl, aryl, aralkyl, heteroaryl, or an amino acid side chain;

wherein R^7 is hydrogen, (C_1 –C_6)alkyl, hydroxy-, alkoxy-, amino-, or alkythio-substituted (C_1 –C_6)alkyl, hydroxy, alkoxy, alkylthio, amino, aryl, aralkyl, heteroaryl, or halogen, and R^8 is hydrogen, (C_1 –C_6) alkyl, hydroxy-, alkoxy-, amino-, or alkythio-substituted (C_1 –C_6)alkyl, aryl, aralkyl, or heteroaryl; or R^7 is hydrogen, (C_1 –C_6)alkyl, hydroxy-, alkoxy-, amino-, or alkythio-substituted (C_1 –C_6)alkyl, alkoxy, aryl, aralkyl, or heteroaryl, and R^8 is hydrogen, (C_1 –C_6)alkyl, hydroxy-, alkoxy-, amino-, or alkythio-substituted (C_1 –C_6)alkyl, hydroxy, alkoxy, alkylthio, amino, aryl, aralkyl, heteroaryl, or halogen;

wherein R^9 is hydrogen, (C_1 –C_6)alkyl, hydroxy-, alkoxy-, amino-, or alkythio-substituted (C_1 –C_6)alkyl, alkoxy, aryl, arylkyl, or heteroaryl;

wherein each of R^{10} and R^{11} is, independently, hydrogen, (C_1 –C_6)alkyl, hydroxy-,

alkoxy-, amino-, or alkythio-substituted (C_1 –C_6)alkyl, aryl, aralkyl, heteroaryl, or an amino acid side chain;

wherein D is a protecting group compatible with the conditions of ester, amide, or phosphonoester bond formation, R^{18}, or $NR^{18}R^{19}$;

wherein E is O^-, OCH_3, a protecting or activating group compatible with ester, phosphoester, or phosphonoester bond formation, R^{20}, $NR^{20}R^{21}$, or OR^{20}; and

wherein each R^{18}, R^{19}, R^{20}, and R^{21} is, independently, hydrogen, (C1-C6)alkyl, an amino protecting group, a reporter group, an intercalator, a chelator, a peptide, a protein, a carbohydrate, a lipid, a steroid, a nucleotide or oligonucleotide, or a soluble or nonsoluble polymer.

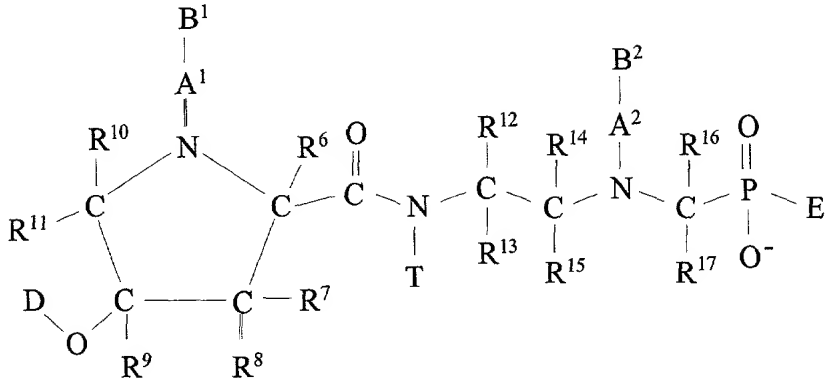
98. The compound of claim 97, wherein D is a protecting group selected from the group consisting of DMTr, MMTr, Tr, TBDMS, or tetraydropyranyl.

99. The compound of claim 97, wherein E is O^-, OH, or OCH_3.

100. The compound of claim 97, wherein B is a nucleobase.

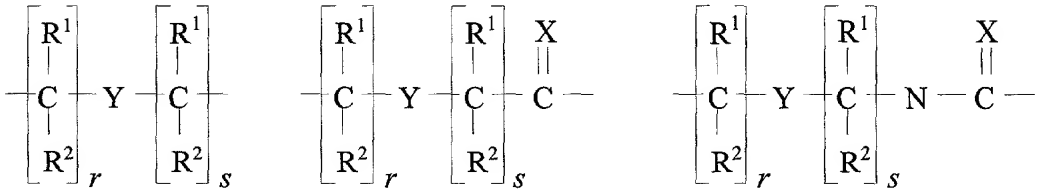
101. The compound of claim 100, wherein B is a naturally-occurring nucleobase.

102. A compound comprising the structure:



wherein each of B^1 and B^2 is, independently, H, a naturally occurring nucleobase, a non-naturally occurring nucleobase, an aromatic moiety, a DNA intercalator, a nucleobase-binding group, a heterocyclic moiety, or a reporter group, wherein amino groups are, optionally, protected by amino protecting groups;

wherein each of A^1 and A^2 is, independently, a group of formula (Ia), (Ib), or (Ic);



I(a) I(b) I(c)

wherein r and s are, for I(a) and I(b), independently of one another, values from 0 to 5 and are, for I(c), independently of one another, values from 1 to 5;

wherein each R^1 and each R^2 is, independently, hydrogen, (C_1 –C_6)alkyl, hydroxy-, alkoxy-, amino-, or alkythio-substituted (C_1 – C_6)alkyl, hydroxy, alkoxy, alkylthio, amino, or halogen;

wherein each R^3, R^4, and R^5, is, independently, hydrogen, (C_1-C_6)alkyl, hydroxy-, alkoxy-, amino-, or alkythio-substituted (C_1-C_6)alkyl, hydroxy, alkoxy, amino, aryl, aralkyl, heteroaryl, or an amino acid side chain;

Y is a single bond, O, S, or NR^4; and

X is O, S, Se, NR^5, CH_2, or $C(CH_3)_2$;

wherein R^6 is hydrogen, (C_1-C_6)alkyl, hydroxy-, alkoxy-, amino-, or alkythio-substituted (C_1-C_6)alkyl, aryl, aralkyl, heteroaryl, or an amino acid side chain;

wherein R^7 is, hydrogen, (C_1-C_6)alkyl, hydroxy-, alkoxy-, amino-, or alkythio-substituted (C_1-C_6)alkyl, hydroxy, alkoxy, alkylthio, amino, aryl, aralkyl, heteroaryl, or hydrogen, and R^8 is hydrogen, (C_1-C_6) alkyl, hydroxy-, alkoxy-, amino-, or alkythio-substituted (C_1-C_6)alkyl, aryl, aralkyl, or heteroaryl; or R^7 is hydrogen, (C_1-C_6)alkyl, hydroxy-, alkoxy-, amino-, or alkythio-substituted (C_1-C_6)alkyl, aryl, aralkyl, or heteroaryl, and R^8 is hydrogen, $(C_1-C_6$)alkyl, hydroxy-, alkoxy-, amino-, or alkythio-substituted $(C_1-C_6$)alkyl, hydroxy, alkoxy, alkylthio, amino, aryl, aralkyl, heteroaryl, or halogen;

wherein R^9 is hydrogen, $(C_1-C_6$)alkyl, hydroxy-, alkoxy-, amino-, or alkythio-substituted $(C_1-C_6$)alkyl, alkoxy, aryl, arylkyl, or heteroaryl;

wherein each of R^{10} and R^{11} is, independently, hydrogen, (C_1-C_6)alkyl, hydroxy-, alkoxy-, amino-, or alkythio-substituted (C_1-C_6)alkyl, aryl, aralkyl, heteroaryl, or an amino acid side chain;

wherein each of R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, and R^{17} is, independently, hydrogen, (C_1 – C_6)alkyl, hydroxy-, alkoxy-, amino-, or alkythio-substituted (C_1 –C_6)alkyl, hydroxy, alkoxy, alkylthio, aryl, aralkyl, heteroaryl, or an amino acid side chain;

wherein D is a protecting group compatible with the conditions of ester, amide, or phosphonoester bond formation, R^{18}, or $NR^{18}R^{19}$;

wherein E is O^-, a protecting or activating group compatible with ester, phosphoester, or phosphonoester bond formation, R^{20}, $NR^{20}R^{21}$, or OR^{20};

wherein T is hydrogen, (C_1 –C_6)alkyl, hydroxy-, alkoxy-, amino-, or alkythio-substituted (C_1 –C_6)alkyl, hydroxy, alkoxy, alkylthio, aryl, aralkyl, heteroaryl, or an amino acid side chain; and

wherein each R^{18}, R^{19}, R^{20}, and R^{21} is, independently, hydrogen, (C1-C6)alkyl, an amino protecting group, a reporter group, an intercalator, a chelator, a linker, a peptide, a protein, a carbohydrate, a lipid, a steroid, a nucleotide or oligonucleotide, or a soluble or nonsoluble polymer.

103. The compound of claim 102, wherein D is a protecting group selected from the group consisting of DMTr, MMTr, Tr, TMDMS, or tetrahydropyranyl.

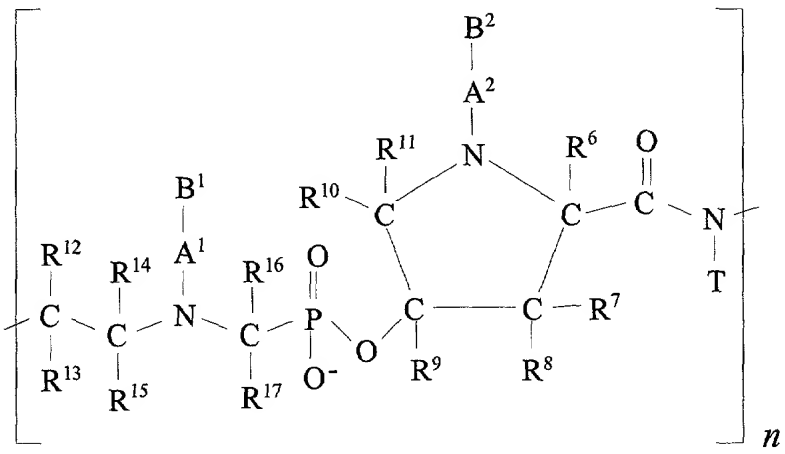
104. The compound of claim 102, wherein E is O^-, OH, 1-oxydo-4-methoxy-2-picolyloxy, phenoxy, 2-methylphenoxy, or 2-cyanoethoxy.

105. The compound of claim 102, wherein T is hydrogen.

106. The compound of claim 102, wherein at least one of B^1 and B^2 is a nucleobase.

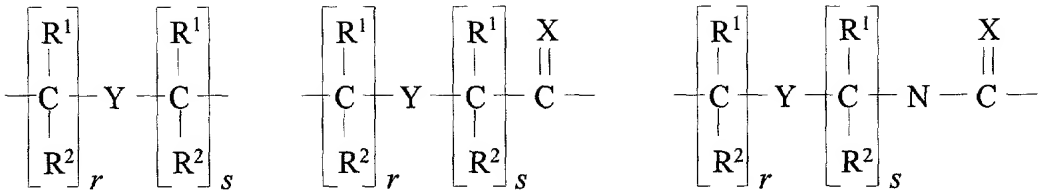
107. The compound of claim 106, wherein at least one of B^1 and B^2 is a naturally-occurring nucleobase.

108. A compound comprising the structure:



wherein each B^1 and each B^2 is, independently, H, a naturally occurring nucleobase, a non-naturally occurring nucleobase, an aromatic moiety, a DNA intercalator, a nucleobase-binding group, a heterocyclic moiety, or a reporter group, wherein amino groups are, optionally, protected by amino protecting groups;

wherein each A^1 and each A^2 is, independently, is a group of formula (Ia), (Ib), or (Ic);



I(a) I(b) I(c)

wherein r and s are, for I(a) and I(b), independently of one another, values from 0 to 5 and are, for I(c), independently of one another, values from 1 to 5;

wherein each R^1 and each R^2 is, independently, hydrogen, (C_1 –C_6)alkyl, hydroxy-, alkoxy-, amino-, or alkythio-substituted (C_1 – C_6)alkyl, hydroxy, alkoxy, alkylthio, amino, or halogen;

wherein each R^3, R^4, and R^5, is, independently, hydrogen, (C_1 –C_6)alkyl, hydroxy-, alkoxy-, amino-, or alkythio-substituted (C_1 – C_6)alkyl, hydroxy, alkoxy, amino, aryl, aralkyl, heteroaryl, or an amino acid side chain;

Y is a single bond, O, S, or NR^4; and

X is O, S, Se, NR^5, CH_2, or $C(CH_3)_2$;

wherein each R^6 is, independently, hydrogen, (C_1 –C_6)alkyl, hydroxy-, alkoxy-, amino-, or alkythio-substituted (C_1 –C_6)alkyl, aryl, aralkyl, heteroaryl, or an amino acid side chain;

wherein R^7 is, independently, hydrogen, (C_1 –C_6)alkyl, hydroxy-, alkoxy-, amino-, or alkythio-substituted (C_1 –C_6)alkyl, hydroxy, alkoxy, alkylthio, amino, aryl,

aralkyl, heteroaryl, or hydrogen, and R^8 is hydrogen, (C_1 –C_6) alkyl, hydroxy-, alkoxy-, amino-, or alkythio-substituted (C_1 –C_6)alkyl, aryl, aralkyl, or heteroaryl; or R^7 is hydrogen, (C_1 –C_6)alkyl, hydroxy-, alkoxy-, amino-, or alkythio-substituted (C_1 –C_6)alkyl, aryl, aralkyl, or heteroaryl, and R^8 is hydrogen, (C_1 –C_6)alkyl, hydroxy-, alkoxy-, amino-, or alkythio-substituted (C_1 –C_6)alkyl, hydroxy, alkoxy, alkylthio, amino, aryl, aralkyl, heteroaryl, or halogen;

wherein each R^9 is independently, hydrogen, (C_1 –C_6)alkyl, hydroxy-, alkoxy-, amino-, or alkythio-substituted (C_1 –C_6)alkyl, alkoxy, aryl, arylkyl, or heteroaryl;

wherein each R^{10} and each R^{11} is, independently, hydrogen, (C_1 –C_6)alkyl, hydroxy-, alkoxy-, amino-, or alkythio-substituted (C_1 –C_6)alkyl, aryl, aralkyl, heteroaryl, or an amino acid side chain;

wherein each R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, and each R^{17} is, independently, hydrogen, (C_1 –C_6)alkyl, hydroxy-, alkoxy-, amino-, or alkythio-substituted (C_1 –C_6)alkyl, hydroxy, alkoxy, alkylthio, aryl, aralkyl, heteroaryl, or an amino acid side chain;

wherein T is hydrogen, (C_1 –C_6)alkyl, hydroxy-, alkoxy-, amino-, or alkythio-substituted (C_1 –C_6)alkyl, hydroxy, alkoxy, alkylthio, aryl, aralkyl, heteroaryl, or an amino acid side chain;

wherein each R^{18}, R^{19}, R^{20}, and R^{21} is, independently, hydrogen, (C1-C6)alkyl, an amino protecting group, a reporter group, an intercalator, a chelator, a linker, a peptide, a protein, a carbohydrate, a lipid, a steroid, a nucleotide or oligonucleotide, or a soluble or nonsoluble polymer; and

n is 1 or greater.

109. The compound of claim 108, further comprising one or more oligonucleotide analogue monomers.

110. The compound of claim 109, wherein at least one of said one or more additional oligonucleotide analogue monomers comprises the compound of claim 1 or a phosphono peptide nucleic acid monomer.

111. The compound of claim 110, wherein the ratio of claim 1 monomers to phosphono peptide nucleic acid monomers is between about 1: 15 and about 5: 3.

112. The compound of claim 108, wherein at least one B^1 or at least one B^2 is a nucleobase.

113. The compound of claim 112, wherein at least one B^1 or at least one B^2 is a naturally-occurring nucleobase.

114. The compound of claim 108 hybridized to a nucleic acid molecule.

115. The compound of claim 109 hybridized to a nucleic acid molecule.

116. The compound of claim 108 bound to a solid support.

117. The compound of claim 109 bound to a solid support.

118. A method for detecting a nucleic acid molecule, comprising:

providing a sample;

contacting the oligonucleotide analogue of claim 108 with said sample under conditions that allow hybridization of nucleic acid molecules with oligonucleotide analogues; and

detecting at least one nucleic acid molecule that hybridizes to said oligonucleotide analogue.

119. The method of claim 118, wherein said oligonucleotide analogue of claim 108 is bound to a solid support.

120. The method of claim 118, wherein said sample comprises DNA.

121. The method of claim 118 wherein said detecting utilizes one or more fluorescent labels.

122. A method for separating, isolating, or purifying at least one nucleic acid molecule from a population of nucleic acid molecules, comprising:

providing a population of nucleic acid molecules;

contacting the population of nucleic acid molecules with one or more capture probes comprising at least one oligonucleotide analogue of claim 12 under conditions that allow hybridization of nucleic acid molecules with oligonucleotide analogues; and

separating at least one nucleic acid molecule that is hybridized to said one or more capture probes from the members of the population of nucleic acid molecules that are not hybridized to said one or more capture probes.

123. The method of claim 122, wherein said population of nucleic acid molecules comprises RNA.

124. The method of claim 122, wherein said one or more capture probes further comprises a specific binding member.

125. The method of claim 122, wherein at least one of said one or more capture probes is a clamping oligoucleotide analogue.

126. The method of claim 122, wherein said one or more capture probes is bound to a solid support.

127. A method for performing homologous recombination, comprising

providing a construct that comprises an oligonucleotide analogue;

introducing said construct into one or more cells;

allowing homologous recombination between said construct and the genome of said one or more cells to occur.

128. The method of claim 127, wherein said construct comprises a peptide nucleic acid, a phosphono peptide nucleic acid, a peptide nucleic acid - phosphono peptide nucleic acid, a hydroxyproline nucleic acid, a serine nucleic acid, a hydroxyproline nucleic acid-peptide nucleic acid, hydroxyproline nucleic acid - phosphono peptide nucleic acid, a serine nucleic acid- peptide nucleic acid , or a serine nucleic acid - phosphono peptide nucleic acid.

129. The method of claim 128, wherein said construct further comprises DNA.

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REMARKS

THE AMENDMENTS TO THE CLAIMS

Applicants have canceled claims 1 through 96 and added claims 97 through 129. These claims add no new subject matter as they are fully supported throughout the specification and the claims as originally filed. This amendment is made for the purpose of economizing on United States Patent and Trademark fees.

CONCLUSION

Applicants respectfully submit that the claims are ready for examination and in condition for allowance. Please apply any charges not covered, or any credits to **Deposit Account 501321 in the name of David R. Preston & Associates having Customer No.: 24232**.

Respectfully submitted,

Date: March 13, 2001

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Reg. No. 38,710

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